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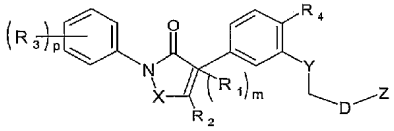
(54) Title: COMPOUNDS HAVING ACTIVITY AT 5HT2C RECEPTOR AND USES THEREOF



(I)

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof are disclosed, wherein $R_1$ is hydrogen, fluoro, chloro, hydroxy, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy or halo$C_{1-6}$alkoxy; m is 0 when ==== is a double bond and m is 1 when ==== is a single bond; $R_2$ is hydrogen, halogen, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group; X is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, $-(CH_2-CH=CH)-$ or a group $-(CHR_5)-$ wherein $R_5$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy or $C_{1-6}$alkylthio; $R_3$ is halogen, cyano, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, halo$C_{1-6}$alkyl, halo$C_{1-6}$alkoxy, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy, aryl$C_{1-6}$alkylthio or $COOR_6$, $CONR_7R_8$ or $COR_9$ wherein $R_6$, $R_7$, $R_8$ and $R_9$ are independently hydrogen or $C_{1-6}$alkyl; p is 0, 1 or 2 or 3; $R_4$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group; Y is oxygen, sulfur, $-CH_2-$ or $NR_{10}$ wherein $R_{10}$ is hydrogen or $C_{1-6}$alkyl; D is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$; and Z is $-NR_{11}R_{12}$ where $R_{11}$ and $R_{12}$ are independently hydrogen or $C_{1-6}$alkyl, or an optionally substituted N-linked or C-linked 4 to 7 membered heterocyclic group. Method of preparation and uses of the compounds in therapy, for example depression and anxiety, are also disclosed.

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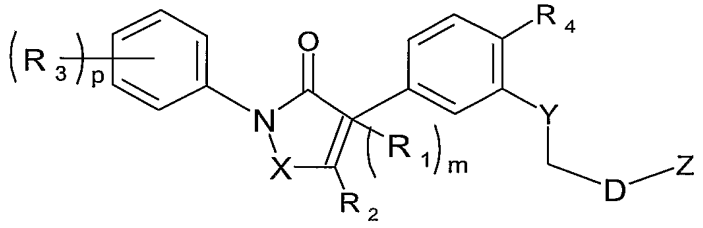
# Compounds having activity at 5HT2c receptor and uses thereof

This invention relates to novel compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 96/23783, WO 97/46699 and WO 97/48700 all disclose a series of indoline derivatives which are 5-$HT_{2C}$ receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders.

A novel class of compounds possessing 5-$HT_{2C}$ receptor activity has been found. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

$R_1$ is hydrogen, fluoro, chloro, hydroxy, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy or halo$C_{1-6}$alkoxy;

m is 0 when ═ is a double bond and m is 1 when ═ is a single bond;

$R_2$ is hydrogen, halogen, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group;

X is $-(CH_2-CH_2)-$, -(CH=CH)-, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, $-(CH_2-CH=CH)-$ or a group $-(CHR_5)-$ wherein $R_5$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy or $C_{1-6}$alkylthio;

$R_3$ is halogen, cyano, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, halo$C_{1-6}$alkyl, halo$C_{1-6}$alkoxy, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy, aryl$C_{1-6}$alkylthio or $COOR_6$, $CONR_7R_8$ or $COR_9$ wherein $R_6$, $R_7$, $R_8$ and $R_9$ are independently hydrogen or $C_{1-6}$alkyl;

p is 0, 1 or 2 or 3;

$R_4$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group;

Y is oxygen, sulfur, $-CH_2-$ or $NR_{10}$ wherein $R_{10}$ is hydrogen or $C_{1-6}$alkyl;

D is a single bond, $-CH_2-$, $-(CH_2)_2-$ or -CH=CH-; and

Z is $-NR_{11}R_{12}$ where $R_{11}$ and $R_{12}$ are independently hydrogen or $C_{1-6}$alkyl, or an optionally substituted N-linked or C-linked 4 to 7 membered heterocyclic group.

The following terms, whether used alone or as part of another group are to be given the following meanings, unless otherwise stated.

The term "halogen" and its abbreviated form "halo" are used herein to describe fluorine, chlorine, bromine or iodine.

The term "alkyl" is used herein to describe a straight chain or branched fully saturated hydrocarbon group. "$C_{1-6}$alkyl" refers to alkyl groups having from one to six carbon atoms, including all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term "$C_{1-6}$alkanoyl" refers to an alkanoyl group having from 1 to 6 carbon atoms, such as methanoyl (or "formyl"), ethanoyl (or "acetyl"), propanoyl, isopropanoyl, butanoyl, isobutanoyl, sec-butanoyl, pentanoyl, neopentanoyl, sec-pentanoyl, isopentanoyl, tertpentanoyl and hexanoyl.

The term "$C_{1-6}$alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, including all isomeric forms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "$C_{3-7}$cycloalkyl" refers to a cycloalkyl group consisting of from 3 to 7 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Optional substituents for $C_{3-7}$cycloalkyl includes one or more halogen, hydroxy, oxo, $C_{1-6}$alkyl, cyano, $CF_3$, $OCF_3$, $C_{1-6}$alkoxy and $C_{1-6}$alkanoyl.

The term "$C_{1-6}$alkylthio" refers to a straight chain or branched chain alkylthio group having from one to six carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio, sec-pentylthio, n-pentylthio, isopentylthio, tert-pentylthio and hexylthio.

The term "mono- or di-$C_{1-6}$alkylamino" refers to an amino group which is substituted by one $C_{1-6}$alkyl group or an amino group which is substituted by two $C_{1-6}$alkyl groups, the two amino groups being the same or different. Examples of monoC1-6alkylamino include methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, tert-butylamine, pentylamine, neopentylamine, sec-pentylamine, n-pentylamine, isopentylamine, tert-pentylamine and hexylamine. Examples of di-C1-6alkylamino include dimethylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, disec-butylamine, ditert-butylamine, dipentylamine,

dineopentylamine, dihexylamine, butylmethylamino, isopropylmethylamino, ethylisopropylamino, ethylmethylamino, etc.

The term "aryl" is used herein to describe groups such as phenyl or naphthyl, which may be optionally substituted by one or more of $C_{1-6}$alkyl (to form "aryl$C_{1-6}$alkyl"), halogen, $CF_3$ or $C_{1-6}$alkoxy (to form "aryl$C_{1-6}$alkoxy").

The terms "halo $C_{1-6}$alkoxy" or "halo$C_{1-6}$alkyl" are used to describe a $C_{1-6}$alkoxy or a $C_{1-6}$alkyl group, respectively, substituted with one or more halogens. Examples include -$CHCl_2$, -$CF_3$, -$OCF_3$, etc.

The term " heterocyclic group" is used herein to describe a stable aromatic or non-aromatic ring containing 1, 2 or 3 heteroatoms selected from nitrogen, sulphur and oxygen. Suitable examples of 4 to 7 membered heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, piperidyl, piperazinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, azepanyl, dioxolanyl, thienyl, tetrahydrothienyl, tetrahydrofuryl, dioxanyl and dithianyl.

The term "N-linked heterocyclic group" is used herein to describe a heterocyclic groupwhich is linked to the remainder of the molecule via a nitrogen atom. Suitable examples of 4 to 7 membered N-linked heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, piperidyl, piperazinyl, morpholinyl and azepanyl.

The term "C-linked heterocyclic group" is used herein to describe a heterocyclic group which is linked to the remainder of the molecule via a carbon atom. Suitable examples of 4 to 7 membered C-linked heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, piperidyl, piperazinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, azepanyl, dioxolanyl, thienyl, tetrahydrothienyl, tetrahyrdofuryl, dioxanyl and dithianyl.

More than one optional substituent may be present in the N-linked or C-linked heterocycle, which may be the same or different, and may be attached to any carbon atom of the heterocycle or an available nitrogen atom.

Suitable optional substituents for the N-linked or C-linked heterocycle include $C_{1-6}$alkyl, amino, mono- or di- $C_{1-6}$alkylamino, aryl, aryl$C_{1-6}$alkyl, arylamino, hydroxy, $C_{1-6}$alkylamido, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkoxycarbonyl, halogen, haloC1-6alkyl, a heteroaromatic group (such as indole or benzimidazole), an aromatic or non-aromatic N-linked or C-linked heterocycle or an aromatic or non-aromatic heterocycle$C_{1-6}$alkyl optionally substituted by $C_{1-6}$alkyl. Examples of aromatic or non-aromatic heterocycle$C_{1-}$

$_6$alkyl include heterocycle-methyl (such as pyridinyl-methyl and benzimidazolyl-methyl) and heterocycle-ethyl (such as morpholinyl-ethyl and indolyl-ethyl).

Substituents in the N-linked or C-linked heterocycle may form a bridge structure, to form a group such as for example 2-oxa-5-azabicyclo[2.2.1]heptyl. Such a bicyclic group may be further substituted by the substituents listed above. More than one substituent may be present on the same carbon atom to form spiro structures such as 1,4 and 1,5 dioxa spiro compounds.

When X is a group -($CHR_5$)-, preferably $R_5$ is hydrogen. Preferably X is -$CH_2$-.

When ═ is a single bond, preferably $R_1$ is hydrogen, hydroxy or $C_{1-6}$alkoxy.

Preferably $R_2$ is hydrogen.

When p is 2 or 3, $R_3$ may be the same or different. Preferably p is 1 or 2 and $R_3$ is/are halogen, particularly chloro or fluoro, attached at the 3 or the 3,4-positions of the phenyl ring.

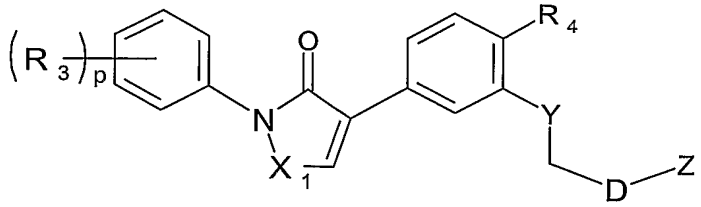
Preferably $R_4$ is $C_{1-6}$alkoxy (particularly methoxy), $OCF_3$, halogen or cyano.

Preferably Y is oxygen.

Preferably D is -$CH_2$-.

Preferably Z is an optionally substituted N-linked 4 to 7 membered heterocycle, in particular piperidyl. Preferred substituents include halogen (particularly fluoro) and $C_{1-6}$alkyl (particularly methyl).

Preferred compounds are compounds of formula (Ia):



(Ia)

wherein $R_3$, p, $R_4$, Y, D, Z, ═ are as defined for formula (I) and $X_1$ is -$CH_2$- or -HC(OH)-. Preferred features of formula (I) also apply to formula (Ia).

Preferred compounds include:

1. 1-(3,4-Dichloro-phenyl)-5-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
2. 1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
3. 1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
4. 1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-methyl-pyrrolidin-2-one
6. 1-(4-Methoxyphenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
7. 1-(4-Methoxyphenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
8. 1-(3-Chloro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
9. 1-(3-Chloro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
10. 1-(3-Fluoro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
11. 1-(3-Fluoro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
12. 1-(3-Fluoro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
13. 1-(3-Fluoro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
14. 1-(3,4-Dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one
15. 1-(3,4-Dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one

and pharmaceutically acceptable salts thereof.

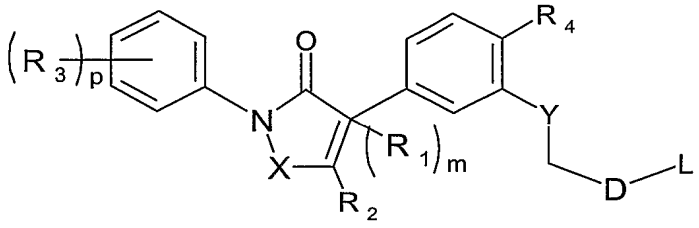
The compounds of formula (I) can form acid addition salts. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric or ("*cis-trans*") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II):



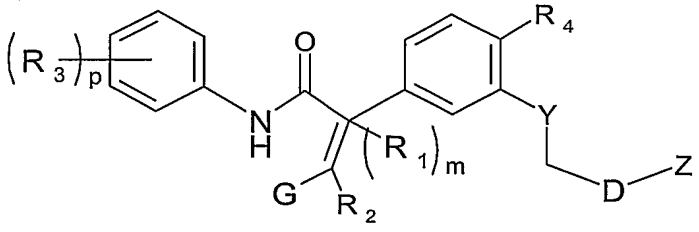
(II)

wherein $R_1$, $R_2$, $R_3$, $R_4$, m, p, X, ═══, Y and D are as defined for formula (I), and L is a leaving group, with a compound of formula (III):

Z-H
(III)

wherein Z is as defined for formula (I); or

(b) cyclising a compound of formula (IV):



(IV)

wherein $R_1$, $R_2$, m, $R_3$, p, R4, Y, D, Z and ═══ are as defined for formula (I) and G is a group -X=$CH_2$, wherein X is as defined for formula (I), dehydrogenated as required;

and thereafter, for either process (a) or process (b), optionally followed by:

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

For the reaction of process (a), suitably L is mesylate. The reaction may take place in a solvent such as DMF in the presence of sodium iodide and potassium carbonate.

The reaction of process (b) suitably takes place in a solvent such as THF in the presence of $OsO_4$ and $NaIO_4$.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, a compound wherein X is -(HCOH)- may be converted to a compound wherein X is -($CH_2$)- by using a suitable reducing agent such as triethylsilane-trifluoroacetic acid using dichloromethane as solvent, and a compound wherein $R_1$ is hydroxy may be converted to compound wherein m is 0 and ═══ is a double bond by an elimination reaction in TFA.

Compounds of formulae (II), (III) and (IV) are commercially available or may be prepared according to methods described herein or may be prepared according to known methods or by analogous methods thereto.

Those skilled in the art will appreciate that it may be necessary to protect certain groups to carry out the above processes. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules,

oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose);, fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate);, tabletting lubricants lubricants (e.g. magnesium stearate, talc or silica);, disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a

surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

The compounds of the present invention have affinity for the 5-$HT_{2C}$ receptor. The affinity can be determined by assessing their ability to displace [$^3$H]-mesulergine from rat or human 5-$HT_{2C}$ clones expressed in 293 cells *in vitro*, as described in WO 94/04533.

All the Example compounds were tested according to this assay and were found to have pKi values >5.8. Some compounds show a considerably higher affinity in the range of 7.0 to >9.0 in human cells.

The intrinsic activity of the compounds of this invention can be determined according to the [$^{35}$S]GTPγS functional assay which is described in WO 99/07700.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the treatment of certain CNS disorders such as depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, vascular dementia with depressed mood, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety including generalised anxiety and social anxiety disorder, schizophrenia, panic disorder, agoraphobia, social phobia, epilepsy, obsessive compulsive disorder and post-traumatic stress disorder, pain (particularly neuropathic pain), migraine, memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof, Alzheimer's disease, motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, disorders associated with spinal trauma and/or head injury such as hydrocephalus, gastrointestinal disorders such as IBS (Irritable Bowel Syndrome), Crohn's disease, ulcerative colitis, non-steroidal anti-inflammatory drug induced damage) as well as microvascular diseases such as macular oedema and retinopathy.

It is to be understood that, as used herein, the term "treatment" refers to alleviation of established symptoms as well as prophylaxis.

Thus the present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance. In particular, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of the above disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a therapeutic substance in the treatment of a CNS disorder. Preferably the CNS disorder is depression or anxiety.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention further provides a method of treatment of the above disorders in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In particular the invention provides a a method of treatment of a CNS disorder in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Preferably the disorder is depression or anxiety.

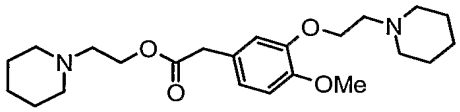
In another aspect, the invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders. In particular the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a CNS disorder. Preferably the CNS disorder is depression or anxiety.

The composition of the present invention may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months. When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the present invention.

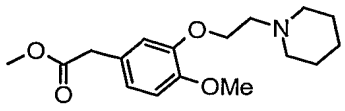
**Preparation 1: [4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetic acid 2-piperidin-1-yl-ethyl ester**



A mixture of (3-hydroxy-4-methoxy-phenyl)-acetic acid (1.85 g), dry DMF (25 ml), $K_2CO_3$ (5.9 g) and *N*-chloroethylpiperidine hydrochloride (3.74 g) was heated at 40 °C for 5 h. Volatiles were then removed *in vacuo* and the residue partitioned between water and EtOAc. The organic layer was washed (brine) and concentrated to give the title (3.76 g) compound as an orange oil.

**NMR ($^1$H, $CDCl_3$):** δ 6.93-6.80 (m, 3H), 4.22 (t, 2H), 4.14 (t, 2H), 3.82 (s, 3H), 3.55 (s, 2H), 2.82 (t, 2H), 2.66-2.40 (m, 10H), 1.66-1.40 (m, 12H).

**Preparation 2: [4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetic acid methyl ester**

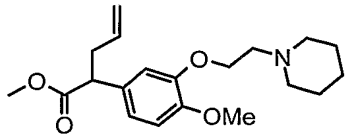


[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetic acid 2-piperidin-1-yl-ethyl ester (6.3 g) in MeOH (6 ml), THF (6 ml) and water (6 ml) containing KOH (1.7 g) was heated at 45 °C for 1 h and then allowed to cool to 25 °C over 90 min. With stirring in an ice bath conc. aqueous HCl (6 ml) was then added. The mixture was evaporated to dryness. The

material was heated at reflux with HCl in MeOH (1 M) for 4 h, concentrated and extracted with $CH_2Cl_2$. The mixture was filtered and the solvent removed *in vacuo* to give the title compound (4.4 g) as an orange oil.

**NMR ($^1$H, $CDCl_3$):** δ 6.88-6.79 (m, 3H), 4.18 (t, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 3.55 (s, 2H), 2.87 (t, 2H), 2.56 (bs, 4H), 1.66 (bs, 4H), 1.46 (bs, 2H).

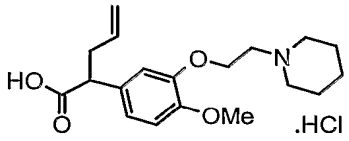
**Preparation 3: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid methyl ester**




**Procedure:** To a solution of [4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetic acid methyl ester (2.1 g) in THF (dry, 15 ml) at –78 °C was slowly added lithium bis(trimethylsilyl)amide (1 M in THF, 8.2 ml). The solution was stirred at this temperature for 15 min before allyl bromide (0.59 ml) was added. After additional 30 min water and EtOAc were added with stirring. The mixture was allowed to warm to 25 °C, layers separated and the organic layer washed (brine), concentrated and submitted to column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give the title compound (1.3 g) as a colourless oil.

**NMR ($^1$H, $CDCl_3$):** δ 6.90-6.80 (m, 3H), 5.76-5.67 (m, 1H), 5.10-4.98 (m, 2H), 4.18 (bs, 2H), 3.83 (s, 3H), 3.65 (s, 3H), 3.56 (t, 1H), 2.86 (bs, 2H), 2.83-2.73 (m, 1H), 2.65-2.45 (m, 5H), 1.65 (bs, 4H), 1.47 (bs, 2H). **MS (*m/z*):** 348 $[MH]^+$.

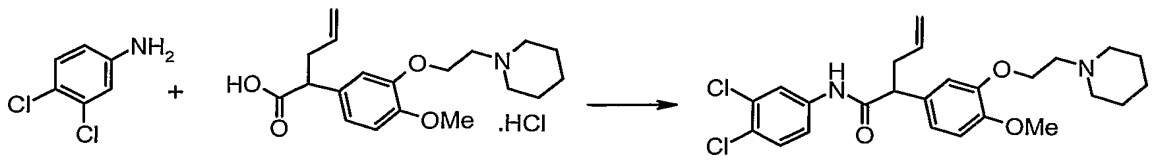
**Preparation 4: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid hydrochloride salt**




2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid methyl ester (1.3 g) in MeOH (2 ml), THF (2 ml) and water (2 ml) containing KOH (0.42 g) was heated at 45 °C for 1 h and then allowed to cool to 25 °C. The mixture was evaporated to dryness. THF (5 ml) and conc. aqueous HCl (0.62 ml) were added, the mixture concentrated, extracted with $CH_2Cl_2$, filtered and the solvent removed *in vacuo* to give the title compound (1.2 g) as an off-white foam.

**NMR ($^1$H, $CD_3OD$):** δ 7.05 (d, 1H), 6.96 (dd, 1H), 6.91 (d, 1H), 5.81-5.70 (m, 1H), 5.02 (dd, 1H), 4.92 (dd, 1H), 4.31 (dd, 2H), 3.83 (s, 3H), 3.48-3.42 (m, 3H), 3.37-3.28 (m, 4H), 2.78-2.69 (m, 1H), 2.44-2.35 (m, 1H), 1.91-1.84 (m, 4H), 1.72-1.63 (m, 2H). **MS (*m/z*):** 334 $[MH]^+$.

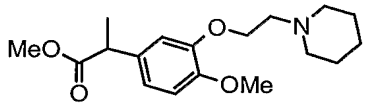
**Preparation 5: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid (3,4-dichlorophenyl)-amide**



To a solution of 2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid hydrochloride salt (0.46 g) in dry $CH_2Cl_2$ (4 ml), under $N_2$, was added, at 0°C, oxalyl chloride (0.11 ml) and DMF (cat). After 30 min the reaction mixture was concentrated to dryness *in vacuo*. To this material was added toluene (dry, 4 ml) and 3,4-dichloroaniline (0.20 g). The mixture was heated at 105 °C for 4 h, then partitioned between aqueous $NaHCO_3$ and EtOAc. The organic layer was washed (brine), concentrated and purified by column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give the title compound (0.35 g) as a slightly brown oil.

**NMR ($^1$H, $CDCl_3$):** δ 7.74 (s, 1H), 7.55 (bs, 1H), 7.31 (bs, 2H), 6.96 (bs, 1H), 6.91-6.83 (m, 2H), 5.77-5.68 (m, 1H), 5.09 (d, 1H), 5.01 (d, 1H), 4.23-4.16 (m, 2H), 3.85 (s, 3H), 3.53 (t, 1H), 2.99-2.91 (m, 1H), 2.83 (t, 2H), 2.55 (bs, 4H), 1.68-1.62 (m, 4H), 1.47 (bs, 3H). **MS (*m/z*):** 477 $[MH]^+$, 2Cl.

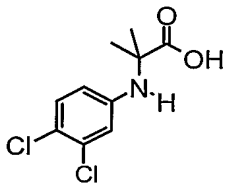
**Preparation 6: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-propanoic acid methyl ester**



To a solution of [4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetic acid methyl ester (0.60 g) in THF (dry, 6 ml) at –78 °C was slowly added lithium bis(trimethylsilyl)amide (1 M in THF, 2.3 ml). The solution was stirred at this temperature for 15 min before iodomethane (0.12 ml) was added, then allowed to warm to 25 °C. After 16 h aqueous $NaHCO_3$ and EtOAc were added with stirring, layers separated and the organic layer washed (brine), concentrated and submitted to column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give the title compound (0.27 g) as a slightly yellow oil.

**NMR ($^1$H, $CD_3OD$):** δ 6.88-6.75 (m, 3H), 4.12 (t, 2H), 3.80 (s, 3H), 3.67-3.34 (m, 4H), 2.78 (t, 2H), 2.50 (bs, 4H), 1.65-1.37 (m, 9H). **MS (*m/z*):** 322 $[MH]^+$.

**Preparation 7: 2-(3,4-Dichloro-phenylamino)-2-methyl-propionic acid**

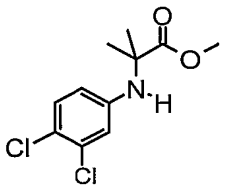


To a solution of 3,4-dichloroaniline (2 g, 12.4 mmol) and 1,1,1-trichloro-2-methyl-2-propanol 0.5 hydrate (3.47 g, 18.63 mmol) in acetone (25 ml) was added KOH (2.79 g,

49.7 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C and overnight at room temperature. The reaction mixture was concentrated *in vacuo*, diluted with water, and washed with diethyl ether. The acqueous solution was acidified with citric acid and extracted with AcOEt (3x150 ml). The organic layer was washed with brine, dried over anhydrous $NaSO_4$ and concentrated *in vacuo* to give the title compound in 2.2 g yield as a white solid (72%).

**NMR ($^1$H, DMSO):** δ 12.30 (bs,1H), 7.18 (d,1H), 6.60 (s, 1H), 6.40 (dd, 1H), 4.98 (bs, 1H), 1.40 (s, 4H).

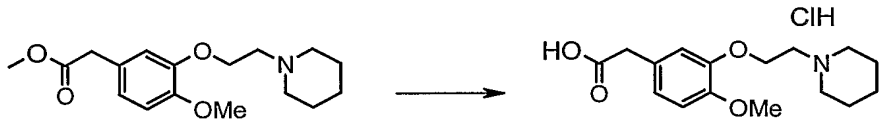
**Preparation 8: Methyl 2-(3,4-dichloro-phenylamino)-2-methyl-propionate**



To a solution of 2-methyl-2-(3,4-dichloroaniline)-propionic acid (0.50 g, 2.02 mmol) in MeOH+$CH_2Cl_2$ (14+7 ml) were added triethylamine (0.57 ml, 4.08 mmol) and $Me_3SiCHN_2$ (2M in hexane, 6.06 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature, concentrated *in vacuo* and the crude product purified by flash chromatography (AcOEt:cyclohexane=1:9) to give the title compound in 489 mg yield as white solid (93%).

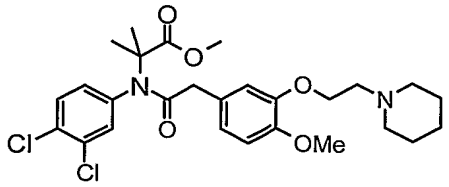
**NMR ($^1$H, DMSO):** δ 7.42 (dd,1H), 6.57 (d, 1H), 6.46 (s, 1H), 6.35 (dd, 1H), 3.62 (s, 3H), 1.45 (s, 6H).

**Preparation 9: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetic acid hydrochloride salt**



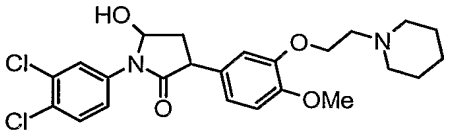
To a solution of methyl-2-(3-[2-piperidin-1-yl-ethoxy]-4-methoxy-phenyl)-acetate (0.59 g, 1.92 mmol) in THF+MeOH (1+1 ml) at 25 °C was added a solution of KOH (0.21 g, 3.84 mmol) in $H_2O$ (1 ml). The solution was heated at 45 °C for 1.5 hours. After removing the solvent *in vacuo* the residue was dissolved in THF and acidified at 0 °C with conc. aqueous HCl. The mixture was concentrated to dryness *in vacuo*, the crude was extracted with PrOH/$CH_2Cl_2$ (1/1), filtered and concentrated to dryness *in vacuo* to give the title compound in 544 mg yield as brown solid (y= 96%). **MS (*m/z*):** 294 $[MH]^+$.

**Preparation 10: 2-((3,4-Dichloro-phenyl)-{2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetyl}-amino)-2-methyl propionic acid methyl ester**



To a solution of 2-(3-[2-piperidin-1-yl-ethoxy]-4-methoxy-phenyl)-acetic acid hydrochloride salt (0.62 g, 1.89 mmol) in $CH_2Cl_2$ (9 ml) at 0 °C were added oxalyl chloride (0.33 ml, 3.78 mmol) and DMF (some drops). The solution was stirred at room temperature for 1.5 hours and concentrated to dryness *in vacuo*. The crude was dissolved in 1,4-dioxane, added with a solution of methyl-2-methyl-2-(3,4-dichloroaniline)-propionate (0.47 g, 1.78 mmol) in 1,4-dioxane and heated at 90 °C for 20 hours. The reaction mixture was concentrated *in vacuo*, dissolved in $CH_2Cl_2$, washed with conc. aqueous $NaHCO_3$, brine and dried over anhydrous $NaSO_4$. After purification by flash chromatography ($CH_2Cl_2$:MeOH=9:1) the title compound was obtained in 681 mg yield as a brown oil (61%). **MS (*m/z*):** 537 $[MH]^+$ (2Cl).

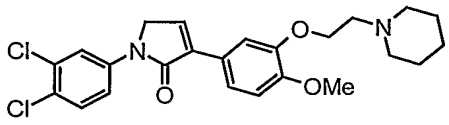
**Example 1: 1-(3,4-Dichloro-phenyl)-5-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one**



To a solution of 2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid (3,4-dichlorophenyl)-amide (0.30 g) in THF/$H_2O$ (5/1, 12 ml) was added $OsO_4$ (4% wt in water, 0.2 ml) and $NaIO_4$ (0.41 g). After 20 hours excess aqueous $Na_2S_2O_3$ was added with stirring. After 5 min. the mixture was partitioned between sat. aqueous $NaHCO_3$ and EtOAc. The organic layer was washed (brine), concentrated to dryness *in vacuo* and the residue purified by column chromatography to give the title product as a colourless foam (0.20 g, *ca.* 2:1 mixture of diastereoisomers):

**NMR ($^1$H, $CDCl_3$):** δ 7.80 and 7.74 (2d, 1H), 7.55-7.35 (m, 2H), 7.00 (s, 0.33H), 6.92 (d, 0.33H), 6.83-6.70 (m, 2.34H), 5.70-5.59 (m, 1H), 4.17-4.00 (m, 3.67H), 3.82 (s, 3H), 3.70 (dd, 0.33H), 2.95-2.85 (m, 0.33H), 2.77 (t, 2H), 2.55-2.34 (m, 5.34H), 2.17-2.08 (m, 0.33H), 1.62-1.50 (m, 4H), 1.46-1.35 (m, 2H). **MS (*m/z*):** 479 $[MH]^+$, 2Cl.

**Example 2: 1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one**

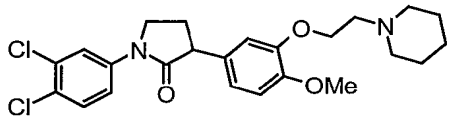


To 1-(3,4-dichloro-phenyl)-5-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one (0.13 g) in $CH_2Cl_2$ (dry, 5 ml) and $Et_3SiH$ (0.13 ml) at 0 °C was added

dropwise a solution of trifluoroacetic acid (0.22 ml) in $CH_2Cl_2$ (dry, 1 ml). The mixture was allowed to warm to 25 °C. After 20 h volatiles were removed *in vacuo* and the residue submitted to column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give a mixture of 1-(3,4-dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one and 1-(3,4-dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one. On trituration with EtOAc : petroleum ether (40-60) 1:2 the title compound was obtained as an off-white solid.

**NMR ($^1$H, $CDCl_3$):** δ 7.99 (d, 1H), 7.70 (dd, 1H), 7.54-7.50 (m, 2H), 7.46 (d, 1H), 7.22 (t, 1H), 6.92 (d, 1H), 4.43 (d, 2H), 4.23 (t, 2H), 3.91 (s, 3H), 2.87 (t, 2H), 2.56 (bs, 4H), 1.70-1.60 (m, 4H), 1.47 (bs, 2H). **MS (*m/z*):** 461 $[MH]^+$, 2Cl. **mp** : 98-99 °C.

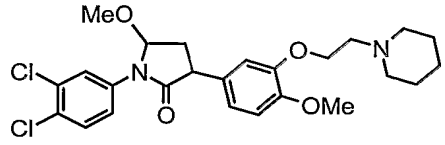
**Example 3: 1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one**




The title compound (22 mg) was obtained as a colourless film from the mother liquor from Example 2 by removal of the volatiles, extraction with hexane and concentration of the hexane solubles *in vacuo*.

**NMR ($^1$H, $CDCl_3$):** δ 7.87 (d, 1H), 7.60 (dd, 1H), 7.43 (d, 1H), 6.89-6.83 (m, 3H), 4.17 (t, 2H), 3.95-3.80 (m, 6H), 2.82 (t, 2H), 2.70-2.60 (m, 1H), 2.52 (bs, 4H), 2.35-2.25 (m, 1H), 1.64-1.58 (m, 4H), 1.50-1.42 (m, 2H). **MS (*m/z*):** 463 $[MH]^+$, 2Cl.

**Example 4: 1-(3,4-Dichloro-phenyl)-5-methoxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one**



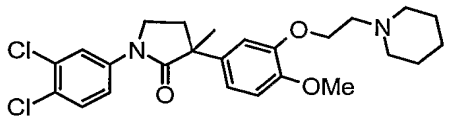

1-(3,4-Dichloro-phenyl)-5-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one was treated with MeOH (dry, 2 ml) containing pyridinium 4-toluenesulfonate (42 mg) at 25 °C for 4 days, at 50 °C for 4 h and at 60 °C for 6 h. The mixture was partitioned between aqueous $NaHCO_3$ and EtOAc. The organic layer was collected, concentrated and submitted to column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$). A major diastereoisomer (3,5-*trans* substitution of the pyrrolidin-2-one, 25 mg slightly yellow film) was isolated besides a *ca.* 1:1 mixture of the major and the minor diastereoisomer (4 mg colourless film) and recovered unreacted starting material (21 mg 1-(3,4-dichloro-phenyl)-5-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one).

**Major diastereoisomer: NMR ($^1$H, $CDCl_3$):** δ 7.81 (d, 1H), 7.51 (d, 1H), 7.45 (d, 1H), 6.90-6.82 (m, 3H), 5.32 (d, 1H), 4.17 (t, 2H), 4.02 (dd, 1H), 3.85 (s, 3H), 3.41 (s, 3H), 2.84

(t, 2H), 2.64 (dd, 1H), 2.56 (bs, 4H), 2.37-2.30 (m, 1H), 1.67-1.60 (m, 4H), 1.50-1.40 (m, 2H). **MS (*m/z*):** 493 $[MH]^+$, 2Cl.

***Ca.* 1:1 mixture of major and minor diastereoisomer: NMR ($^1$H, $CDCl_3$):** δ 7.82 and 7.74 (2d, 1H), 7.51 (d, 0.5H), 7.48-7.42 (m, 1H), 7.03 (d, 0.5H), 6.97 (dd, 0.5 H), 6.91-6.83 (m, 2.5H), 5.37-5.33 (m, 1H), 4.26-4.20 (m, 2H), 4.02 (dd, 0.5H), 3.85 (2s, 3H), 3.77 (dd, 0.5H), 3.41 and 3.38 (2s, 3H), 2.89 (bs, 2H), 2.85-2.78 (m, 0.5H), 2.70-2.50 (m, 4.5H), 2.37-2.24 (m, 1H), 1.66 (bs, 4H), 1.48 (bs, 2H). **MS (*m/z*):** 493 $[MH]^+$, 2Cl.

**Example 5: 1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-methyl-pyrrolidin-2-one**




To a solution of 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-propanoic acid methyl ester (0.27 g) in THF (dry, 5 ml) at –78 °C was slowly added lithium bis(trimethylsilyl)amide (1 M in THF, 1.0 ml). The solution was stirred at this temperature for 15 min before allyl bromide (0.11 ml) was added. The mixture was allowed to warm to 0 °C and kept at that temperature for 1.5 h. It was then partitioned between aqueous $NaHCO_3$ and EtOAc, layers separated and the organic layer washed (brine), concentrated and submitted to column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give a colourless oil (0.14 g).

This material in MeOH (1 ml) containing KOH (5 eq.) was heated at 45 °C for 3 h and then and then kept at 25 °C for 18 h. The mixture was evaporated to dryness. Excess aqueous HCl was added, the mixture concentrated, extracted with $CH_2Cl_2$, filtered and the solvent removed *in vacuo* to give a colourless foam (0.09 g).

To this material in dry $CH_2Cl_2$ (1 ml), under $N_2$, was added, at 0 °C, oxalyl chloride (0.03 ml) and DMF (cat). After 1 h the reaction mixture was concentrated to dryness *in vacuo*. To this material was added dioxane (dry, 1 ml) and 3,4-dichloroaniline (0.04 g). The mixture was heated at 95 °C for 4 h, concentrated *in vacuo* and purified by column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give an orange oil (0.06 g).

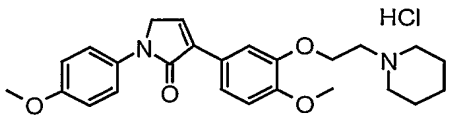
This material was converted to 1-(3,4-dichloro-phenyl)-5-hydroxy-3-methyl-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one (37 mg colourless film) in analogy to the procedure described for Example 1.

To 1-(3,4-dichloro-phenyl)-5-hydroxy-3-methyl-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one (30 mg) in $CH_2Cl_2$ (dry, 0.5 ml) and $Et_3SiH$ (0.049 ml) was added dropwise a solution of trifluoroacetic acid (0.047 ml) in $CH_2Cl_2$ (dry, 0.5 ml) at 0 °C. The mixture was allowed to warm to 25 °C. After 7.5 h volatiles were removed *in vacuo* and the residue submitted to column chromatography (silica gel, $CH_2Cl_2$ / MeOH / $NH_3$) to give the title compound (19 mg) as a colourless film.

**NMR ($^1$H, $CDCl_3$):** δ 7.88 (d, 1H), 7.57 (dd, 1H), 7.41 (d, 1H), 7.01 (d, 1H), 6.92 (dd, 1H), 6.82 (d, 1H), 4.14 (t, 2H), 3.84 (s, 3H), 3.75-3.66 (m, 2H), 2.79 (t, 2H), 2.64-2.57 (m, 1H),

2.58 (bs, 4H), 2.29-2.21 (m, 1H), 1.65-1.55 (m, 7H), 1.50-1.40 (m, 2H). **MS (*m/z*):** 477 $[MH]^+$, 2Cl.

**Example 6: 1-(4-Methoxyphenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one hydrochloride**



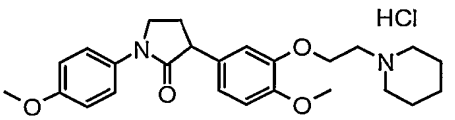

To a solution of 2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pent-4-enoic acid (4-methoxyphenyl)-amide (prepared in an analogous way to Procedure 5, 570 mg, 1.3 mmol) in acetone/$H_2O$ 8/1 (33 ml) was added N-methyl-morpholine-N-oxide (2eq, 304 mg) and $OsO_4$ (4wt% sol. in water, cat., 0.84 ml). The reaction was stirred at room temperature for 6 hours and then quenched with 40 ml of $Na_2SO_3$ sat. After 15 minutes stirring the diol was extracted with ethyl acetate (2x20 ml), dried over $Na_2SO_4$, filtered and concentrated to dryness *in vacuo*.

The crude product was then dissolved in THF/$H_2O$ 1/1 (30 ml) and potassium periodate (1.5 eq, 391 mg) was added. The reaction mixture was stirred at room temperature for 3 hours. The solution was diluted with water (20 ml) and extracted with ethyl acetate (3x20 ml). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated to dryness *in vacuo*. Flash chromatography of the crude product (silica gel, $CH_2Cl_2$/MeOH/$NH_3$ aq. 150/10/1) gave 245 mg of the cyclized product.

This material (130 mg) was dissolved in TFA (2.5 ml). The reaction mixture was stirred at room temperature for 2 hours, then concentrated *in vacuo*. A saturated solution of $NaHCO_3$ was added and the mixture was extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ and HCl (1M in $Et_2O$, 2 ml) was added, the volatiles evaporated and the residue triturated with $Et_2O$ to give 130 mg of the title product as a light pink solid:

**NMR ($^1$H, DMSO-d6):** δ 9.9 (bs 1H), 7.71 (d, 2H), 7.7-6.64 (m, 2H), 7.67 (t, 1H), 7.09 (d, 1H), 6.99 (d, 2H), 4.56 (d, 2H), 4.39 (bt, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.58 (m, 2H), 3.50 (m, 2H), 3.04 (m, 2H), 1.81 (m, 4H), 1.7 (m, 1H), 1.4 (m, 1H). **MS (*m/z*):** 423 $[MH]^+$.

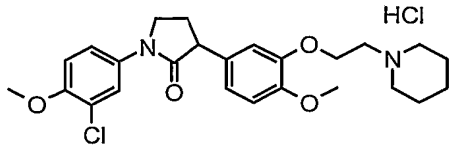
**Example 7: 1-(4-Methoxyphenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one hydrochloride**




The product was prepared in an analogous way to the one described for Example 3.

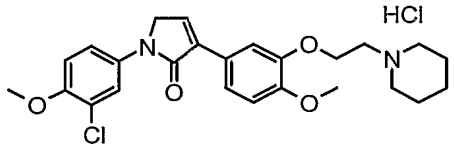
**NMR ($^1$H, DMSO-d6):** δ 9.87 (bs, 1H), 7.58 (d, 2H), 7.0-6.8 (m, 5H), 4.33 (t, 2H), 3.85 (m, 2H), 3.84 (t, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.55 (d, 2H) 3.45 (m, 2H), 3.02 (m, 2H), 2.53 (m, 1H), 2.16 (m, 1H), 1.85-1.65 (m, 5H), 1.39 (m, 1H). **MS (*m/z*):** 425 $[MH]^+$.

**Example 8: 1-(3-Chloro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one hydrochloride**



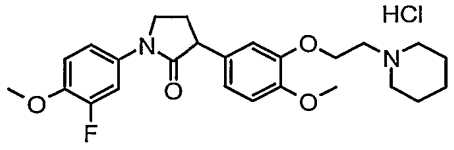

The product was prepared in an analogous way to the one described for Example 3.
**NMR ($^1$H, DMSO-d6):** δ 9.75 (bs, 1H), 7.89 (d, 1H), 7.53 (dd, 1H), 7.17 (d, 1H), 6.99 (m, 2H), 6.90 (dd, 1H), 4.32 (t, 2H), 3.87 (m, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.55 (m, 2H), 3.45 (m, 2H), 3.0 (m, 2H), 2.5 (m, 1H), 2.15 (m, 1H), 1.9 (m, 4H), 1.4 (m, 2H). **MS (*m/z*):** 459 $[MH]^+$, 1Cl.

**Example 9: 1-(3-Chloro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one hydrochloride**




The product was prepared in an analogous way to the one described for Example 6.
**NMR ($^1$H, DMSO-d6):** δ 9.76 (bs, 1H), 8.01 (d, 1H), 7.68 (m, 4H), 7.19 (d, 1H), 7.08 (d, 1H), 4.59 (d, 2H), 4.38 (t, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.58 (m, 2H), 3.50 (m, 2H), 3.04 (m, 2H), 1.85 (m, 4H), 1.4 (m, 2H). **MS (*m/z*):** 457 $[MH]^+$, 1Cl.

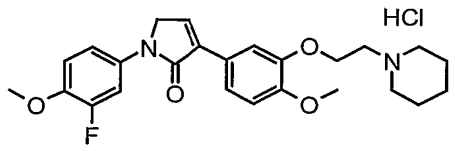
**Example 10: 1-(3-Fluoro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one hydrochloride**




The product was prepared in an analogous way to the one described for Example 3.
**NMR ($^1$H, DMSO-d6):** δ 9.82 (bs, 1H), 7.74 (dd, 1H), 7.36 (dd, 1H), 7.17 (t, 1H), 6.99 (m, 2H), 6.90 (dd, 1H), 4.32 (t, 2H), 3.87 (m, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.54 (m, 2H), 3.45

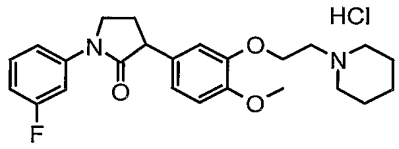
(m, 2H), 3.0 (m, 2H), 2.5 (m, 1H), 2.16 (m, 1H), 1.85 (m, 4H), 1.4 (m, 2H). **MS (*m/z*):** 443 $[MH]^+$.

**Example 11: 1-(3-Fluoro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one hydrochloride**



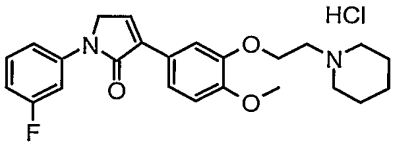

The product was prepared in an analogous way to the one described for Example 6.
**NMR ($^1$H, DMSO-d6):** δ 9.87 (bs, 1H), 7.84 (dd, 1H), 7.68 (m, 2H), 7.66 (dd, 1H), 7.51 (m, 1H), 7.21 (t, 1H), 7.08 (d, 1H), 4.58 (d, 2H), 4.39 (t, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.57 (bd, 2H), 3.49 (m, 2H), 3.04 (m, 2H), 1.9-1.75 (m, 5H), 1.4 (m, 1H). **MS (*m/z*):** 441 $[MH]^+$.

**Example 12: 1-(3-Fluoro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one hydrochloride**



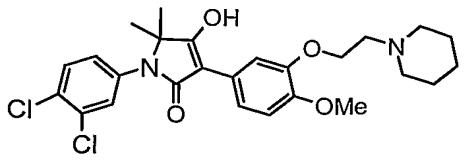

The product was prepared in an analogous way to the one described for Example 3.
**NMR ($^1$H, DMSO-d6):** δ 9.75 (bs, 1H), 7.70 (m, 1H), 7.47 (m, 1H), 7.43 (m, 1H), 7.0 (m, 1H), 7.0 (m, 2H), 6.92 (dd, 1H), 4.32 (t, 2H), 3.90 (m, 3H), 3.77 (s, 3H), 3.54 (m, 2H), 3.46 (m, 2H), 3.0 (m, 2H), 2.5-2.2 (m, 2H), 1.82 (m, 4H), 1.4 (m, 2H). **MS (*m/z*):** 413 $[MH]^+$.

**Example 13: 1-(3-Fluoro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one hydrochloride**




The product was prepared in an analogous way to the one described for Example 6.
**NMR ($^1$H, DMSO-d6):** δ 9.9 (bs, 1H), 7.82 (m, 1H), 7.73 (t, 1H), 7.66 (m, 2H), 7.60 (dd, 1H), 7.45 (m, 1H), 7.09 (d, 1H), 6.97 (m, 1H), 4.62 (d, 2H), 4.39 (t, 2H), 3.82 (s, 3H), 3.57 (m, 2H), 3.48 (m, 2H), 3.02 (m, 2H), 1.9 (m, 4H), 1.4 (m, 2H). **MS (*m/z*):** 411 $[MH]^+$.

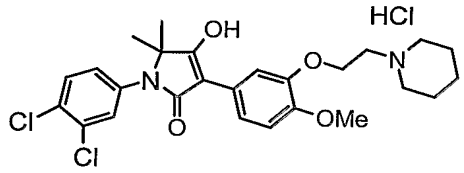
**Example 14: 1-(3,4-Dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one**



To a solution of 2-((3,4-dichloro-phenyl)-{2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetyl}-amino)-2-methyl propionic acid methyl ester (0.19 g, 0.35 mmol) in $CH_2Cl_2$+THF (1.5+1.5 ml) at 0 °C was added NaH (60% in mineral oil, 13.9 mg, 0.35 mmol). The solution was stirred at room temperature for 1.5 hours, cooled at 0 °C and HCl (1M in $Et_2O$, 0.35 mmol) was added. After stirring the solution at room temperature for 15 minutes, the solvent was removed *in vacuo*, the crude was dissolved in $CH_2Cl_2$, filtered and concentrated to dryness *in vacuo*. After purification by flash chromatography $CH_2Cl_2$:MeOH=(9:1) the title compound was obtained in 143 mg yield as a yellow solid (82%).

**NMR ($^1$H, DMSO):** δ 9.50 (bs,1H), 8.16 (bs, 1H), 7.97 (bd, 1H), 7.83 (d, 1H), 7.53 (d, 1H), 7.34 (dd, 1H), 6.87 (d, 1H), 4.21 (t, 2H), 3.83 (t, 2H), 3.69 (s, 3H), 3.27 (m, 4H), 1.71 (m, 4H), 1.50 (bm, 2H), 1.25 (s, 6H). **MS (*m/z*):** 505 $[MH]^+$ (2Cl).

**Example 15: 1-(3,4-Dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one hydrochloride salt**

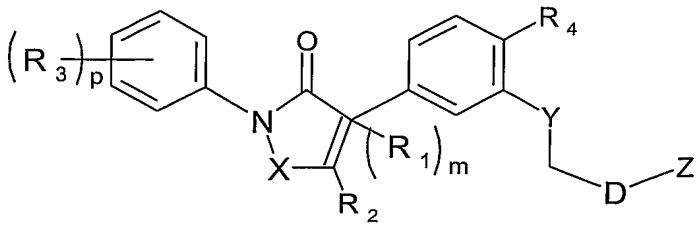


To a solution of 1-(3,4-dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one in $CH_2Cl_2$ was added excess HCl (1M in $Et_2O$). The resulting mixture was evaporated to dryness and the residue triturated with $Et_2O$ and dried to give the title compound in 5 mg yield as a white solid (66%).

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

wherein:



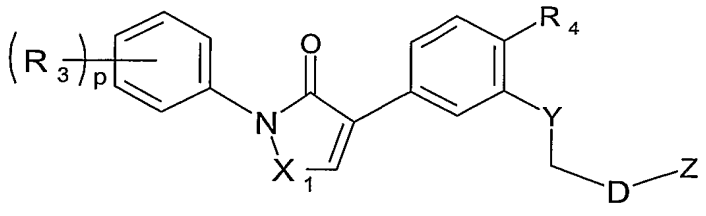
(I)

$R_1$ is hydrogen, fluoro, chloro, hydroxy, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy or halo$C_{1-6}$alkoxy;
m is 0 when ═ is a double bond and m is 1 when ═ is a single bond;
$R_2$ is hydrogen, halogen, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group;
X is $-(CH_2-CH_2)-$, -(CH=CH)-, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, $-(CH_2-CH=CH)-$ or a group $-(CHR_5)-$ wherein $R_5$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy or $C_{1-6}$alkylthio;
$R_3$ is halogen, cyano, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, halo$C_{1-6}$alkyl, halo$C_{1-6}$alkoxy, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy, aryl$C_{1-6}$alkylthio or $COOR_6$, $CONR_7R_8$ or $COR_9$ wherein $R_6$, $R_7$, $R_8$ and $R_9$ are independently hydrogen or $C_{1-6}$alkyl;
p is 0, 1 or 2 or 3;
$R_4$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group;
Y is oxygen, sulfur, $-CH_2-$ or $NR_{10}$ wherein $R_{10}$ is hydrogen or $C_{1-6}$alkyl;
D is a single bond, $-CH_2-$, $-(CH_2)_2-$ or -CH=CH-; and
Z is $-NR_{11}R_{12}$ where $R_{11}$ and $R_{12}$ are independently hydrogen or $C_{1-6}$alkyl, or an optionally substituted N-linked or C-linked 4 to 7 membered heterocyclic group.

2. A compound as claimed in claim 1, wherein X is $-CH_2-$.

3. A compound as claimed in claim 1 or claim 2, wherein when ═ is a single bond, $R_1$ is hydrogen, hydroxy or $C_{1-6}$alkoxy.

4. A compound as claimed in claim 1 having the following formula (Ia):



(Ia)

wherein $R_3$, p, $R_4$, Y, D, Z, ═ are as defined in claim 1, 2 or 3 and $X_1$ is $-CH_2-$ or -HC(OH)-.

5. A compound as claimed in any of claims 1-4, wherein p is 1 or 2 and $R_3$ is/are halogen, particularly chloro or fluoro, attached at the 3 or the 3,4-positions of the phenyl ring.

6. A compound as claimed in any of claims 1-5, wherein $R_4$ is $C_{1-6}$alkoxy (particularly methoxy), $OCF_3$, halogen or cyano.

7. A compound as claimed in any of claims 1-6, wherein D is $-CH_2-$.

8. A compound as claimed in any of claims 1-7, wherein Y is oxygen.

9. A compound as claimed in any of claims 1-8, wherein Z is an optionally substituted N-linked 4 to 7 membered heterocycle.

10. A compound as claimed in claim 9, wherein Z is piperidyl.

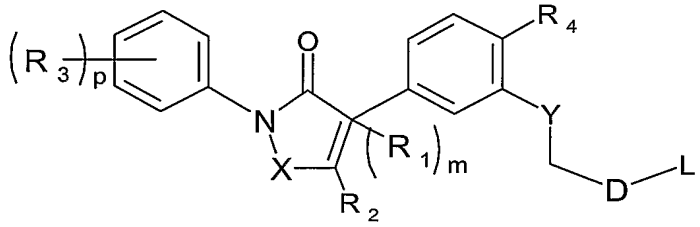
11. A compound as claimed in claim 1 which is:

1-(3,4-Dichloro-phenyl)-5-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-(3,4-Dichloro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-methyl-pyrrolidin-2-one
1-(4-Methoxyphenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
1-(4-Methoxyphenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one

1-(3-Chloro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-(3-Chloro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
1-(3-Fluoro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-(3-Fluoro-4-methoxy-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
1-(3-Fluoro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrolidin-2-one
1-(3-Fluoro-phenyl)-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-1,5-dihydro-pyrrole-2-one
1-(3,4-Dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one
1-(3,4-Dichloro-phenyl)-5,5-dimethyl-4-hydroxy-3-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-pyrrol-2-one or a pharmaceutically acceptable salt thereof.

12. A process for the preparation of a compound as defined in any of claims 1-11, which process comprises:

(a) reacting a compound of formula (II):

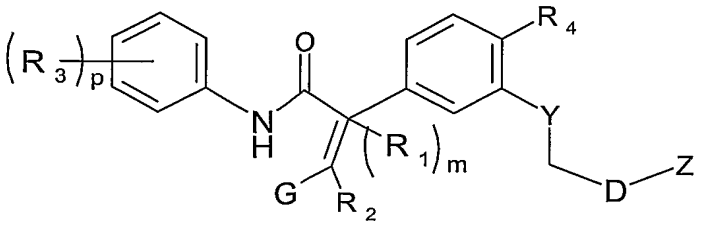


(II)

wherein $R_1$, $R_2$, $R_3$, $R_4$, m, p, X, ═══, Y and D are as defined for formula (I), and L is a leaving group, with a compound of formula (III):

Z-H
(III)

wherein Z is as defined for formula (I); or



(IV)

(b) cyclising a compound of formula (IV):

wherein $R_1$, $R_2$, m, $R_3$, p, R4, Y, D, Z and ═ are as defined for formula (I) and G is a group -X=$CH_2$, wherein X is as defined for formula (I), dehydrogenated as required;

and thereafter, for either process (a) or process (b), optionally followed by:

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

13. A pharmaceutical composition comprising a compound as defined in any of claims 1-14 and a pharmaceutically acceptable carrier or excipient.

14. A process for preparing a pharmaceutical composition as defined in claim 13, the process comprising mixing a compound a compound as defined in any of claims 1-14 and a pharmaceutically acceptable carrier or excipient.

15. A compound as defined in any of claims 1-11 for use as a therapeutic substance.

16. A compound as defined in any of claims 1-11 for use in the treatment of a CNS disorder.

17. A compound as defined in any of claims 1-11 for use in the treatment of depression or anxiety.

18. A method of treatment of CNS disorder in a mammal including a human, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as defined in any of claims 1-11.

19. A method of treatment of depression or anxiety in a mammal including a human, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as defined in any of claims 1-11.

20. Use of a compound as defined in any of claims 1-11 in the manufacture of a medicament for use in the treatment of a CNS disorder.

21. The use of a compound as defined in any of claims 1-11 in the manufacture of a medicament for use in the treatment of depression or anxiety.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001843

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/26 C07D207/38 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 01/96308 A (RIVERS LEANNE ; SMITH TERENCE (GB); GROOM ANTHONY JOHN (GB); HATAKEYAM) 20 December 2001 (2001-12-20) abstract; tables | 1-21 |
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 22 July 2004 | 30/07/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Frelon, D |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001843

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/001843

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/001843

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(25) Filing Language: English

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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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(75) Inventors/Applicants *(for US only)*: **DAMIANI, Federica** [IT/IT]; GlaxoSmithkline, Via Alessandro Fleming 2, I-37135 Verona (IT). **HAMPRECHT, Dieter** [DE/IT]; GlaxoSmithkline, Via Alessandro Fleming 2, I-37135 Verona (IT). **MICHELI, Fabrizio** [IT/IT]; GlaxoSmithkline, Via Alessandro Fleming 2, I-37135 Verona (IT). **PASQUARELLO, Alessandra** [IT/IT]; GlaxoSmithkline, Via Alessandro Fleming 2, I-37135 Verona (IT). **TEDESCO, Giovanna** [IT/IT]; GlaxoSmithkline, Via Alessandro Fleming 2, I-37135 Verona (IT).

(74) Agent: **KONDO, Rie**; GlaxoSmithkline, CIP (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(15) Information about Correction:
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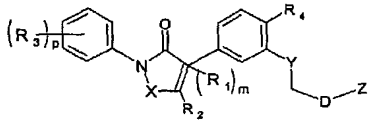
*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMPOUNDS HAVING ACTIVITY AT 5HT2C RECEPTOR AND USES THEREOF



(I)

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof are disclosed, wherein $R_1$ is hydrogen, fluoro, chloro, hydroxy, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy or halo$C_{1-6}$alkoxy; m is 0 when ==== is a double bond and m is 1 when ==== is a single bond; $R_2$ is hydrogen, halogen, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group; X is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, $-(CH_2-CH=CH)-$ or a group $-(CHR_5)-$ wherein $R_5$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy or $C_{1-6}$alkylthio; $R_3$ is halogen, cyano, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, halo$C_{1-6}$alkyl, halo$C_{1-6}$alkoxy, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy, aryl$C_{1-6}$alkylthio or $COOR_6$, $CONR_7R_8$ or $COR_9$ wherein $R_6$, $R_7$, $R_8$ and $R_9$ are independently hydrogen or $C_{1-6}$alkyl; p is 0, 1 or 2 or 3; $R_4$ is hydrogen, halogen, hydroxy, cyano, nitro, $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyloxy, halo$C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo$C_{1-6}$alkoxy, $C_{1-6}$alkylthio, amino, mono- or di-$C_{1-6}$alkylamino or an N-linked 4 to 7 membered heterocyclic group; Y is oxygen, sulfur, $-CH_2-$ or $NR_{10}$ wherein $R_{10}$ is hydrogen or $C_{1-6}$alkyl; D is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$; and Z is $-NR_{11}R_{12}$ where $R_{11}$ and $R_{12}$ are independently hydrogen or $C_{1-6}$alkyl, or an optionally substituted N-linked or C-linked 4 to 7 membered heterocyclic group. Method of preparation and uses of the compounds in therapy, for example depression and anxiety, are also disclosed.

WO 2004/078718 A1

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001843

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/26 C07D207/38 A61K31/40

**corrected version**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 01/96308 A (RIVERS LEANNE ; SMITH TERENCE (GB); GROOM ANTHONY JOHN (GB); HATAKEYAM) 20 December 2001 (2001-12-20) abstract; tables | 1-21 |
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| A,P | WO 03/089409 A (GLAXO GROUP LTD ; JAXA-CHAMIEC ALBERT ANDRZEJ (IT); DAMIANI FEDERICA () 30 October 2003 (2003-10-30) | |

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| 22 July 2004 | 11. 02. 2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
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Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001843

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/001843

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP[illegible]/001843

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